

**Amendments to the Claims:**

This listing of Claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently Amended) A method of monitoring ~~progression of a~~ changes in xenograft metabolism in a non-human host animal comprising:
  - (i) genetically modifying ~~or engineering~~ a cell before or after implantation into an animal so as to incorporate at least one reporter molecule and/or reporter gene and/or reporter agent into said cell;
  - (ii) implanting said modified cell into said host animal and allowing a xenograft to grow for a sufficient period of time; and
  - (iii) measuring at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene that is secreted into the blood or excreted in a body product.
2. (Previously Presented) The method according to claim 1 wherein there is a plurality of genetically modified or engineered cells which are human or non-human in origin.
3. (Previously Presented) The method according to claim 1 wherein the cell is a primary isolate derived from normal tissue or a tumor or is an immortalized or established cell line.
4. (Previously Presented) The method according to claim 1 wherein the reporter molecule is selected from the group consisting of a protein, an antigen, an enzyme, an enzyme substrate, a fluorescent agent, a chemiluminescent agent, a chromogenic agent and a radionuclide.
5. (Previously Presented) The method according to claim 1 wherein the reporter gene is selected from those genes encoding proteins chloramphenicol-acetyltransferase,  $\beta$ -

galactosidase,  $\beta$ -glucuronidase, luciferase, beta-galactosidase or green fluorescent protein, secreted alkaline phosphatase (SEAP), major urinary protein (MUP) or human chorionic gonadotrophin (hCG).

6. (Previously Presented) The method according to claim 1 where the reporter agent is a protease or kinase or the reporter is a protein or RNA effecting changes in protein or mRNA stabilization.

7. (Previously Presented) The method according to claim 1 wherein the host animal is a rodent.

8. (Previously Presented) The method according to claim 7 wherein the rodent is a mouse or rat.

9. (Previously Presented) The method according to claim 7 wherein the rodent is a wild type or genetically engineered mouse or rat having a specifically selected genetic background.

10. (Previously Presented) The method according to claim 1 wherein the host animal has more than one different population of reporter cells/system implanted therein.

11. (Currently Amended) The method according to claim 1 wherein the step comprising measuring at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule, reporter gene or reporter agent is a qualitative or quantitative measurement and optionally comprises invasive or non-invasive procedures for making the measurement.

12. (Previously Presented) The method according to claim 1 wherein the xenograft proliferates as a xenograft tumor with or without metastatic tumors at secondary sites.

13. (Previously Presented) The method according to claim 1 wherein the implanted modified cells are introduced into the host animal either as individual cells suspended in a suitable medium or as tumor fragments.

14. (Previously Presented) The method according to claim 1 wherein the implanted modified cells grow in the host animal either systemically or as a xenograft tumor at the site of implantation.

15. (Previously Presented) The method according to claim 1 wherein the host animal is (i) immunosuppressed by a method comprising administration of appropriate immunosuppressant agents, (ii) an immunocompromised strain or (iii) immunologically intact and wherein the implanted modified cell is synergistic with the host animal.

16. (Previously Presented) The method according to claim 1 wherein the reporter cell/system is genetically engineered to express a transgene or multiple transgenes.

17. (Previously Presented) The method according to claim 1 wherein the reporter cell/system expresses the reporter gene(s) or agent(s) at the time of implantation or is transfected *in vivo* with the reporter gene or agent in a specifically targeted manner.

18. (Previously Presented) The method according to claim 1 wherein the reporter gene(s) or agent(s) comprise at least one element that allows measurement of a biochemical parameter in response to either changes in cell physiology occurring during reporter cell/system proliferation or as a result of toxicological or pharmacological effects of an administered xenobiotic-compound or biological substance.

19. (Previously Presented) The method according to claim 1 wherein the step of measuring at least one parameter of a selected biochemical/ physiological response associated

with the reporter molecule, reporter gene or reporter agent comprises measuring or monitoring any one or more of the following parameters:

- (a) reporter cell numbers, cell cycle modulation or mitotic fraction, cell differentiation, angiogenesis, hypoxia, cell death by necrosis, cell lysis or apoptosis;
- (b) oxidative stress, DNA damage, mitochondrial function, membrane perturbation, GSH depletion, receptor-mediated toxicity, enzyme inhibition, cofactor availability, pH or osmotic change, perturbation of calcium homeostasis, cell differentiation, protein turnover, ubiquitination or protein misfolding;
- (c) effects on intracellular signalling pathways, receptor interactions, effects on gene transcription, translation or protein stability, hormone or growth factor receptor modulation, peroxisome proliferator-activated receptor modulation, intracellular signal transduction pathways, MAP kinase or phosphatase signalling, p53 signalling or ras signalling; or
- (d) induction of drug resistance mechanisms, drug delivery or drug bystander effects.

20. (Previously Presented) The method according to claim 1 wherein the reporter gene comprises a naturally occurring or artificial promoter sequence driving expression of a gene resulting in production of a reporter protein.

21. (Previously Presented) The method according to claim 20 wherein the promoter is constitutively active or is inducible.

22. (Previously Presented) The method according to claim 1 wherein the reporter gene expression product is reportable transcriptionally or post-transcriptionally.

23. (Previously Presented) The method according to claim 22 wherein transcriptional reporting is mediated by any one of the gene promoters selected from the group consisting of vascular endothelial growth factor (VEGF), nitric oxide synthetase (iNOS) promoter, haemoxygenase-1 (HO-1) promoter, cyclo-oxygenase-2 (COX-2) promoter, transglutaminase promoter, Peg3/pw1 promoter, 14-3-3 protein promoter and a GADD153 promoter.

24. (Previously Presented) The method according to claim 22 wherein post-transcriptional reporting is mediated through generation of a protein that can effect protein modifications selected from the group consisting of a consequence of protease activity that results in translocation of a cytoplasmic protein to the nucleus or from membrane-bound form to secreted form, protein cleavage, activation of a proenzyme or transcription factor, deactivation of an active enzyme or transcription factor and secretion into the blood or excretion into urine.

25. (Previously Presented) The method according to claim 22 wherein post-transcriptional reporting is mediated through production of a protein or RNA that effects changes in the stabilization of a protein or mRNA.

26. (Previously Presented) The method according to claim 22 wherein post-transcriptional reporting is mediated through production of a protein ~~which on~~ expressed upon death or lysis of a ~~[[the]]~~ cell expressing said protein ~~[[it]]~~.

27. (Previously Presented) The method according to claim 1 wherein measuring of at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene or reporter agent comprises a non-invasive or an invasive assay wherein:

(i) the non-invasive assay is in excreted body products, or by bioluminescence measurement, or by blood pressure measurement, or by transcutaneous oxygen tension measurement, or by nuclear magnetic resonance measurement or by positron emission tomographic measurement; or

- (ii) an invasive assay for blood or xenograft reporter products.

28. (Currently Amended) The product produced by the method of claim 1 and comprising a genetically modified ~~or engineered~~ cell, the modification ~~or engineering~~ of the cell being such that the cell comprises at least one reporter molecule or reporter gene.

29 - 32. (Canceled)

33. (Canceled)

34. (Previously Presented) The method of claim 1 further comprising:

- (a) measuring reporter cell proliferation, in response to treatments;
- (b) determining the mechanism of differentiation or death where reporter cell differentiation or death occurs;
- (c) monitoring processes in secondary metastatic tumors;
- (d) making non-invasive measurements of parameters related to biochemical processes in the reporter cell/system;
- (e) identifying drug-resistant cell populations;
- (f) determining the effects of genetic background on tumor cell growth or on response to treatments;
- (g) making dynamic measurements using reporter molecules or genes of short half lives or that are excreted;
- (h) determining or confirming the targets of drug action *in vivo*;
- (i) measuring drug bystander effects; and identifying promoter elements involved in gene regulation;
- (j) determining intracellular drug concentrations and thereby those cells that take up a drug; and
- (k) determining or confirming the targets of drug action *in vivo*.

35-36. (Canceled)

37. (New) The method of claim 1, wherein measuring at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene comprises multiple measurements made over a protracted period of time.